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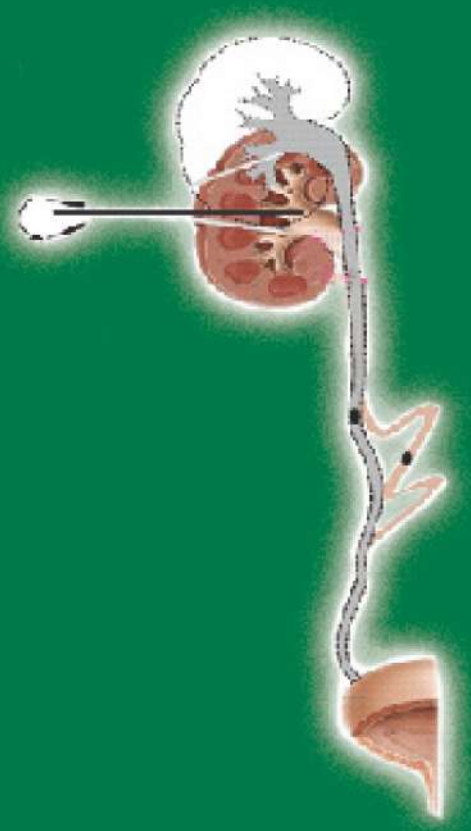

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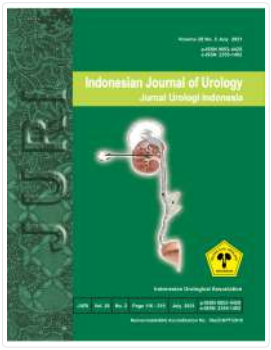

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THE EFFICACY COMPARISON OF MIRABEGRON AS A MONOTHERAPY VERSUS ITS COMBINATION WITH SOLIFENACIN IN OVERACTIVE BLADDER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Objective: *This review aimed to evaluate the efficacy and safety of mirabegron as monotherapy and its combination with solifenacin for patients with overactive bladder (OAB).* ***Material & Methods:*** *A systematic search was conducted in PubMed, Google Scholar, and Science Direct using the keywords Overactive bladder or OAB and mirabegron or beta-3 agonist or β3 adrenoreceptor agonist and solifenacin or antimuscarinic based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline to include relevant randomized controlled trials (RCT)s. The included studies were assessed for their risks of bias using the Cochrane risk of bias tool for randomized controlled trials. Quantitative analysis using forest plot was performed in Review Manager 5.4.* ***Results:*** *A total of 4 RCTs were included from 227 studies. A fixed-effects model was chosen due to the low level of heterogeneity between the studies (I^2 = 0%). The average micturition volume of patients in the combination group is higher compared to the monotherapy group (MD 17.13, 95% CI 12.78 - 21.48, p < 0.00001). The mean micturition frequency (MD - 0.54, 95% CI - 0.73 - -0.34, p < 0.00001) and incontinence incidence (MD -0.30, 95% CI -0.48 - -0.12, p = 0.001) in the combined group are significantly lower compared to the monotherapy group.* ***Conclusion:*** *The combination of mirabegron and solifenacin has better efficacy compared to mirabegron as monotherapy for OAB patients with a therapy duration of less than 12 weeks based on the micturition volume, micturition frequency, and incontinence incidence. The administration of combination therapy would not increase adverse event incidence compared to monotherapy.*

Keywords: *Overactive bladder, beta-3 agonist, mirabegron, solifenacin.*

ABSTRAK

Tujuan: *Telaah sistematis dan meta-analisis ini bertujuan untuk mengetahui efikasi dan keamanan mirabegron sebagai monoterapi dan kombinasinya dengan solifenacin untuk pasien overactive bladder (OAB).* ***Bahan & Cara:*** *Pencarian sistematis dilakukan pada database ilmiah PubMed, MEDLINE, ScienceDirect, dan Google Scholar menggunakan kata kunci Overactive bladder atau OAB dan mirabegron atau beta-3 agonist atau β3 adrenoceptor agonist dan solifenacin atau antimuscarinic untuk mencari studi uji klinis acak yang relevan berdasarkan panduan dari PRISMA. Potensi bias dari studi yang terpilih dievaluasi menggunakan Cochrane Risk of Bias tool for Randomized Trials. Meta analisis dengan forest plot dilakukan menggunakan program Review Manager (RevMan) versi 5.4.* ***Hasil:*** *Dari 227 studi yang didapatkan, 4 studi memenuhi kriteria inklusi dan memiliki risiko bias yang rendah. Seluruh analisis forest plot untuk tiap variabel menunjukkan heterogenitas yang rendah (I^2 = 0%), sehingga dilakuan analisis dengan menggunakan model fixed effects. Hasil rata-rata volume miksi pasien pada grup kombinasi lebih tinggi dibanding monoterapi (MD 17.13, 95% CI 12.78-21.48, p < 0.00001). Hasil rata-rata frekuensi miksi (MD -0.54, 95% CI -0.73 - -0.34, p < 0.00001) dan inkontinensia (MD -0.30, 95% CI -0.48 - -0.12, p = 0.001) pada kelompok kombinasi lebih rendah dibanding kelompok monoterapi secara signifikan. Tidak terdapat perbedaan yang signifikan dalam efek samping antara kedua kelompok (OR 2.07 95% CI 1.39-3.07, p = 0.0003).* ***Simpulan:*** *Kombinasi terapi mirabegron dan solifenacin memiliki efikasi yang lebih baik dibandingkan monoterapi mirabegron pada pasien OAB dengan durasi terapi 12 minggu berdasarkan volume miksi, frekuensi berkemih, dan inkontinensia. Pemberian kombinasi terapi tersebut tidak menimbulkan peningkatan efek samping dibanding monoterapi.*

Kata Kunci: *Overactive bladder, beta-3 agonist, mirabegron, solifenacin.*

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INTRODUCTION

Overactive bladder (OAB) is a condition that comprises a collection of symptoms related to urgency, incontinence, nocturia, and an increase in micturition frequency or a combination of the symptoms. Even though OAB is not directly linked to mortality, untreated cases may affect the quality of life of patients. A study in Europe evaluating 16.000 adult patients more than 40 years of age claimed that 17% of subjects were suffering from OAB, with frequency as the most common symptom. However, 40% of subjects never came to the doctor for their complaints as some accepted the condition as either non-lethal or normal among the elderlies, even though the symptoms were perceived as bothersome.[1]

The etiology of OAB varies. One of the believed hypothesis is that there is the neuroplasticity of the nerves which lead to early pathological bladder contraction. Neuroplasticity phenomenon is common among patients with Diabetes Mellitus or other diseases which may damage the peripheral nervous system.[2]

Pharmacological therapy for OAB includes antimuscarinic drugs (solifenacin, propiverine, and trospium) and β3-adrenoreceptor agonists (mirabegron).[3] Even though antimuscarinic and mirabegron have similar efficacy, the incidence of adverse events differs between the two drug types, in which antimuscarinics usually cause more adverse events.[4] Therefore, currently mirabegron is chosen as the primary therapy for OAB. Among several patients receiving pharmacological therapy, the alleviation of OAB symptoms was minimally felt. However, attempting to increase the dose would usually increase adverse events without reducing the symptoms.[5]

Therefore, other alternatives are to combine both drugs. The combination of the two drugs is expected to generate more benefits compared to monotherapy. The efficacy of the treatment can be evaluated from the micturition volume, frequency, incontinence frequency, urgency, nocturia, and potential adverse events.

OBJECTIVE

This systematic review and meta-analysis aimed to evaluate the comparison of efficacy between mirabegron as monotherapy and its combination with solifenacin for OAB patients.

MATERIAL & METHODS

We performed a systematic search in the PUBMED, ScienceDirect, and Google Scholar databases. The search and screening process was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to look for randomized controlled trials (RCTs) measuring the difference in efficacy between mirabegron as a monotherapy and the combination of mirabegron and solifenacin. The keywords used were: overactive bladder OR OAB) AND (mirabegron OR beta-3 agonist OR β3 adrenoceptor agonist) AND (solifenacin OR antimuscarinic) AND "clinical trial". The measured outcomes were: micturition volume, frequency, incontinence, and adverse events.

This meta-analysis included only randomized controlled trial design studies which

Table 1. Inclusion and exclusion criteria of the research.

Inclusion	Exclusion
Randomized controlled trials (RCTs)	Research in the form of abstract only
Studies comparing mirabegron and combination of mirabegron and solifenacin for OAB	Studies comparing different interventions
Studies with 2 arms or more	Studies only evaluating one arm
Patients with OAB	Patients with OAB and other coexisting abnormalities
	Foreign language
	Observational studies
	In-vitro and animal studies
	Unpublished or ongoing results

compare laser to pneumatic lithotripsy. Case-control, cross-sectional, cohort, and non-randomized controlled trials were excluded. The inclusion and exclusion criteria are presented in table 1.

Data were independently extracted from each study applying a standardized form by all reviewers and all the disparency of the reviewers was solved by discussion. If the reviewers could not reach a consensus, another author was consulted to resolve the dispute and a final decision was made by the majority of votes.

The risk of bias of the studies was performed to determine the quality of each included study. The studies were evaluated using the Cochrane risk of bias tools (RoB) for a randomized trial, which assessed several parameters: selection bias, performance bias, detection bias, reporting bias, and incomplete outcomes. This review did not use other tools as the included studies were all RCTs.

Every included article was presented in the baseline characteristics table. The studies' authors, year, country, study design, the sample size in each arm, treatment, duration of therapy, mean age, and sex are reported for each study. Quantitative analysis was performed using a pooled analysis comparing variables for each study. The samples were divided into mirabegron monotherapy and a combination of both therapy groups. Continuous data were presented as mean and standard deviation, in which the difference was compared between each study for the pre and post-intervention of each outcome. Dichotomous data from the proportion and sample size was analyzed as odds ratio for the adverse event. A fixed-effects model was used for a low level of heterogeneity among the studies ($I^2 < 50\%$), whereas a random-effects model, was used for a high level of heterogeneity ($I^2 > 50\%$). The analysis was performed using Review Manager 5.4.

RESULTS

A total of 4 studies were included in this meta-analysis. The data from each study was analyzed and presented in the forest plot. Heterogenous research data was analyzed using a random-effects model, whereas homogenous data was analyzed using a fixed-effects model. The flow of this research is briefly described in the prism flowchart in figure 1.

Every included study was analyzed both qualitatively and quantitatively as well as presented as a tabulation in Table 2. There are 2033 patients from 4 studies.

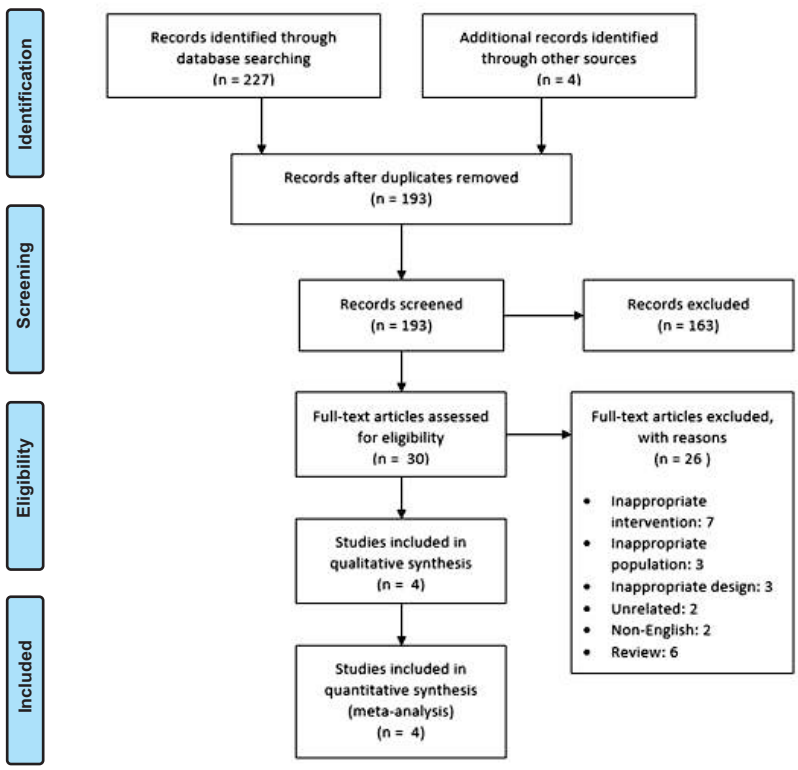

Figure 1. PRISMA diagram describing the systematic search and screening process.

Table 2. Studies' Baseline Characteristics

Author, year	Country	Study Design	Treatment	Treatment Duration (weeks)	Sample Size	Mean Age (Years)	Sex
Abrams, 2014	Multicenter, more than 20 countries	RCT phase 2	• Plasebo • Solifenacin 2.5 mg • Solifenacin 5 mg • Solifenacin 10 mg • Mirabegron 25 mg • Mirabegron 50 mg • Solifenacin 2.5 mg + mirabegron 25 mg • Solifenacin 5 mg + mirabegron 25 mg • Solifenacin 10 mg + mirabegron 25 mg • Solifenacin 2,5 mg + mirabegron 50 mg • Solifenacin 5 mg + mirabegron 50 mg • Solifenacin 10 mg + mirabegron 50 mg	12	1306	54.92	Male and female
Kosilov, 2015	Russia	RCT	• Solifenacin 10 mg • Mirabegron 50 mg • Solifenacin 10 mg + mirabegron 50 mg	6	239	71.2	Male and female
Herschorn , 2017	Multicenter Multinational	RCT phase 3	• Plasebo • Solifenacin 5 mg • Mirabegron 25 mg • Mirabegron 50 mg • Solifenacin 5 mg + mirabegron 25 mg • Solifenacin 5 mg + mirabegron 50 mg	12	3398	57.4	Male and female
Gratzke, 2018	Multinasional multicenter	RCT phase 3	• Solifenacin 5 mg • Mirabegron 50 mg • Solifenacin 5 mg + mirabegron 50 mg	12	1829	60.33	Male and female

The analysis of the risk of bias used the Cochrane risk of bias tool for randomized trials. Three studies by Abrams et al, Herschorn et al, and Gratzke et al have low overall risks of bias.[6-8] One study by Kosilov et al showed some concerns of bias, possibly due to a shorter therapy duration of only six weeks. Randomization process and blinding was implemented in all studies

The 6772 samples in this study were divided into the pneumatic and laser lithotripsy groups. From the overall meta-analysis, the data is quite homogeneous based on the results from I2, which was < 50%, thus a fixed-effect model was used for the meta-analyses. The outcomes assessed in this meta-analysis were micturition volume, micturition frequency, incontinence rate, and adverse events.

There are 3 studies evaluating the micturition volume of mirabegron and solifenacin combination compared to mirabegron monotherapy. Pooled analysis showed that the studies were homogenous ($T^2 = 0\%$, $p = 0.89$). Analysis was therefore performed using the fixed-effects model. The combination therapy showed favorable results compared to monotherapy as shown in figure 3 (MD 17.13, 95% CI = 12.78-21.48, $p < 0.00001$).

Figure 2. Risk of bias assessment of the included studies.

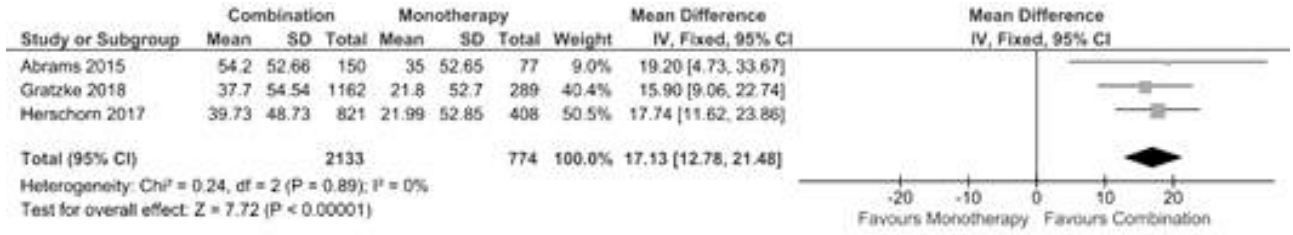

Figure 3. Forest plot analysis showing a significantly higher micturition volume among the combination group compared to the monotherapy group.

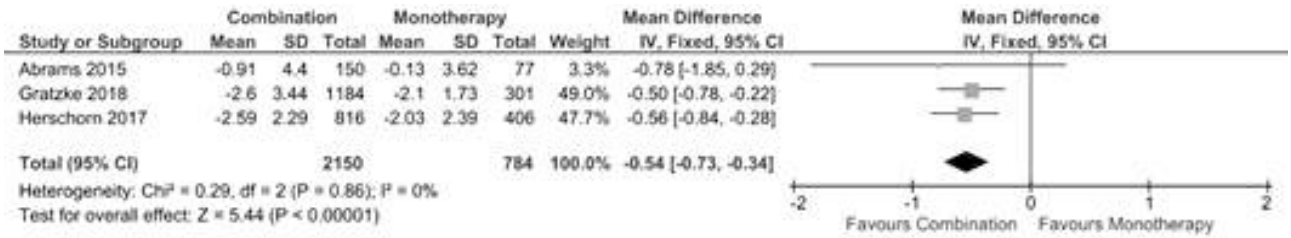

Figure 4. Forest plot analysis showing a significantly lower micturition frequencyamong the combination group compared to the monotherapy group.

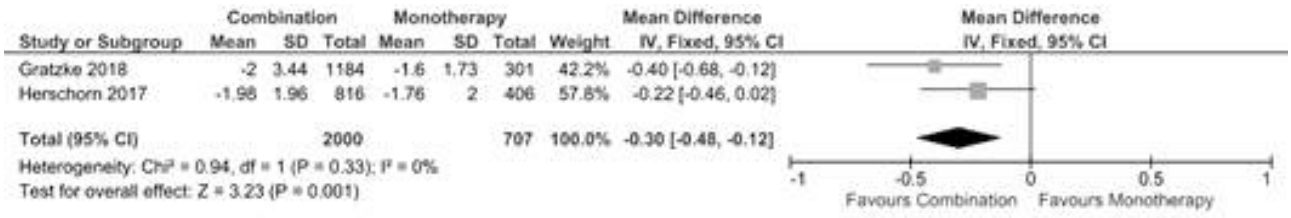

Figure 5. Forest plot analysis showing a significantly incontinence incidence among the combination group compared to the monotherapy group.

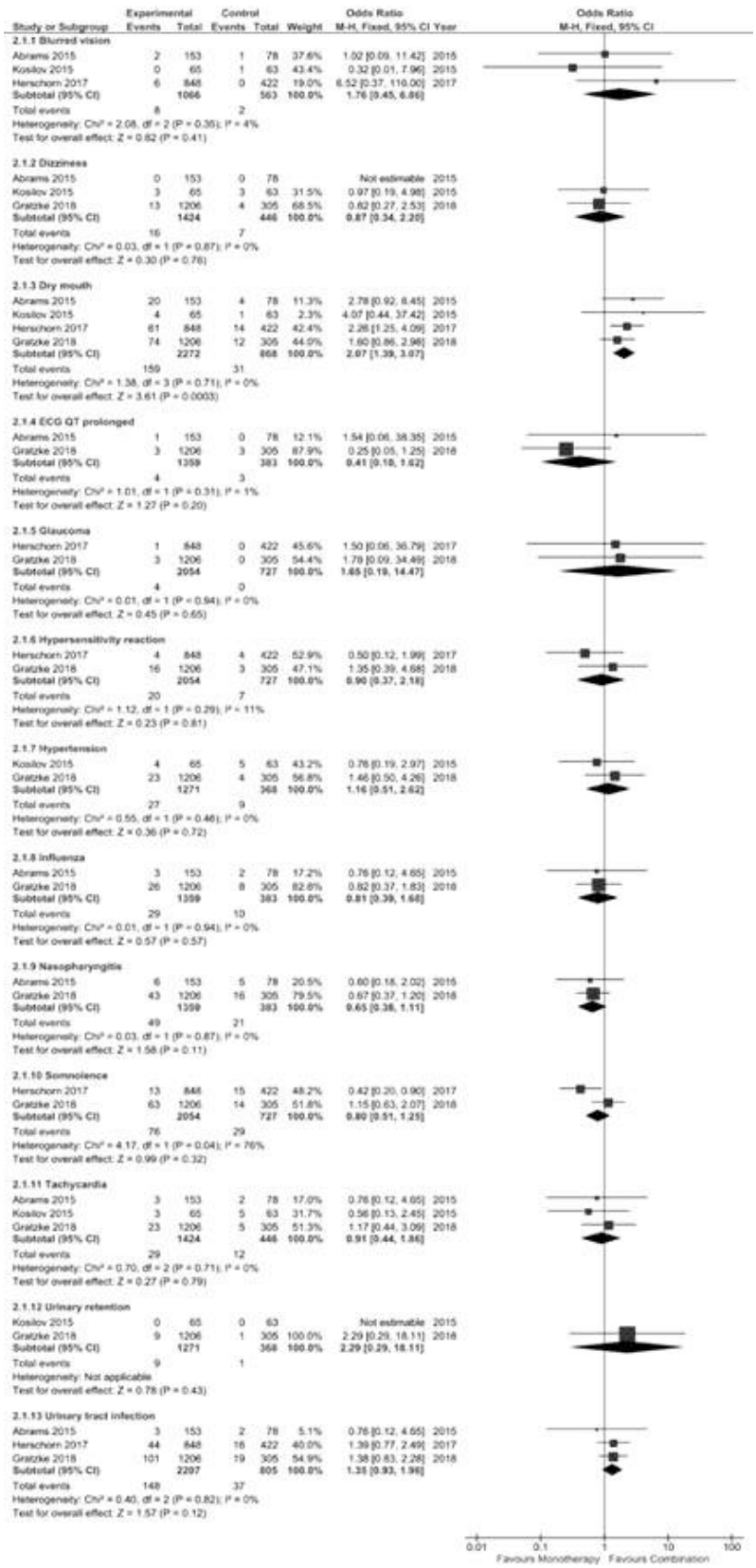

Figure 6. Forest plot analysis of adverse events between both groups.

There are 3 studies evaluating micturition frequency of mirabegron and solifenacin combination compared to mirabegron monotherapy. Pooled analysis results showed homogeneity (I^2 = 0%, p = 0.52). As the samples were homogeneous, a fixed-effects model was used. The forest plot analysis in figure 4 showed a significantly lower micturition frequency among the combination group compared to the monotherapy group (MD -0.54, 95% CI = -0.73 - -0.34, p < 0.00001).

There are 2 studies evaluating the incontinence incidence between the groups. Pooled analysis results showed a low level of heterogeneity (I^2 = 0%, p = 0.33), leading to a fixed-effects model analysis. The incidence of incontinence was significantly lower in the combination group compared to the monotherapy group (MD -0.30, 95% CI -0.48 - -0.12, p = 0.001) as shown in figure 5.

There are 4 studies evaluating the adverse events between the groups. The extracted and analyzed variables were blurry vision, dizziness, dry mouth, prolonged QT wave in ECG, glaucoma, hypersensitivity, hypertension, influenza, nasopharyngitis, somnolence, tachycardia, urinary retention, and urinary tract infection. Out of the 13 adverse events, dry mouth was the only significant event in the combination group (OR 2.07, 95% CI 1.39 – 3.07, p = 0.0003) with a low level of heterogeneity (I^2 = 0%) as shown in figure 6.

DISCUSSION

Mirabegron is one of the latest B3-adrenoreceptor agonists to treat OAB. Other alternatives for treating OAB, include antimuscarinic type drugs. Solifenacin is one of the types usually used for urge incontinence as well as OAB. Due to the different mechanisms of action between the two drugs, several publications recommend combining the two to increase efficacy in treatment. The principle of OAB treatment with pharmacotherapy is divided into two approaches to the autonomic nervous system, parasympathetic and sympathetic. The parasympathetic mechanism involves the binding of acetylcholine with the M3 receptor of the bladder causing detrusor muscle contraction. The administration of antimuscarinic drugs like solifenacin prevents the binding of acetylcholine with the M3 receptor, thus decreasing detrusor muscle contraction. The administration of B3 adrenoreceptor agonist like mirabegron leads to the relaxation of the detrusor muscle.[9]

In this meta-analysis, the dose of mirabegron and solifenacin from the trials was 50 mg and 5 mg respectively based on the recommendation by The Indonesian Continence Society (PERKINA).[10] The SCORPI trial has shown that the administration of 50 mg mirabegron can alleviate symptoms on the 4th week until one year of treatment.[11] The BEYOND trial also showed the alleviation of frequency, urgency, and incontinence by administering the same dose compared to the placebo group.[12] The administration of a lower dose of the drug was shown to lessen the probability of treatment success. Only around two-thirds of OAB patients receiving 25 mg of mirabegron showed improvement of symptoms.[13] A prospective study that included 251 OAB patients showed that 25 mg Mirabegron was severely limited in terms of treatment response, in which significant response was only seen in nocturia complaints.[14] Solifenacin is usually used as an alternative to mirabegron. The usual dose is 5 to 40 mg with an increasing effect as the dose is increased.

In a phase 3 RCT evaluating 2800 patients, 5 mg solifenacin was shown to alleviate urgency, frequency, incontinence, and nocturia symptoms.[15] High dose solifenacin can be administered for patients with severe OAB, however the SUNRISE trial showed that 10 mg solifenacin showed insignificant difference compared to 5 mg solifenacin.[16] Other studies also advised against the administration of 5 mg solifenacin to patients with chronic kidney disease, hepatic abnormalities, and patients receiving CYP3A4 inhibitors.[17] The findings are in line with the dose used in the included RCTS, which was 5 mg. The combination of solifenacin and mirabegron offers better clinical improvement compared to mirabegron monotherapy for patients with OAB in this study. Previous studies showed similar results which explained that the combination of 50 mg mirabegron and 2.5 mg solifenacin offered better improvement among OAB patients receiving either 5 mg or 10 mg mirabegron monotherapy.[18]

There are three variables of efficacy evaluated in this review: micturition volume, micturition frequency, and incontinence incidence. The conclusion of the three included studies indicated that combination therapy provided better outcomes compared to monotherapy. The forest plot analysis in this study also showed that mirabegron and solifenacin combination has significantly better efficacy in all measured outcomes compared to

mirabegron monotherapy. A study by Krauwinkel et al. showed that from a pharmacokinetic point of view, the interaction between mirabegron and solifenacin is not clinically relevant.[19]

The aim of administering a combination therapy is to increase the pharmacokinetic synergic effect while decreasing adverse events caused by each drug by administering a lower dose compared to a monotherapy dose. Drake et al claimed that the combination therapy of 50 mg mirabegron and 5 mg solifenacin offered better clinical improvements and tolerability in OAB patients compared to either 5 mg or 10 mg solifenacin monotherapy.[20]

However, a network meta-analysis concluded that monotherapy mirabegron therapy showed significant improvements compared to the combination of the two drugs.[21] Aside from efficacy, the key to a successful OAB treatment is the low occurrence of adverse events considering the patient would require long-term therapy. The presence of B3 receptors in cardiovascular tissues raises concerns of possible cardiovascular effects from mirabegron. Antimuscarinic, on the other hand, may cause adverse events due to the M3 receptor blockade. M3 receptors are present in salivary glands and the lining of the gastrointestinal tract causing possible dry mouth and constipation when blocked.[22]

There are 13 adverse events evaluated in this study, among which, dry mouth was the only significant adverse event found to be significantly higher among the combination therapy compared to the monotherapy. This is expected, as dry mouth is caused by the action of the antimuscarinic agent. Other adverse events were found in both groups without any significant difference. Previous studies claimed that combining mirabegron and solifenacin would result in more adverse events compared to mirabegron monotherapy.[6,8]

In this study, the only apparent adverse event higher in the combination group is dry mouth. The differences in the trials included in this review may be different due to methodological and sample size differences between the studies. However, the previous systematic review evaluating similar interventions also showed an insignificant difference in adverse events between the groups.[23] This review is limited by the lack of information regarding the difference of sex between male and female among the samples.

Considering the difference of OAB presentation based on sex, evaluation of response to therapy should also be taken into account. Future studies should evaluate specific populations based on certain specific characteristics to prevent biases that may arise from particular characteristics.

CONCLUSION

The combination therapy of mirabegron and solifenacin offers better efficacy compared to mirabegron monotherapy for OAB patients. There is no significant difference of adverse events between the combination therapy and monotherapy apart from dry mouth among the combination group.

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